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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/535,262	03/23/00	LANG	X	GTSYS.003.A

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EXAMINER	
EINSMANN, J	
ART UNIT	**PAPER NUMBER**
1655	8

DATE MAILED: 01/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/535,262	LANG ET AL.	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☒ Claim(s) 7-8 is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5+6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite over the recitation of the parenthetical in line 2 of the claim. This is indefinite because the relationship between the PNA molecule via a linker and the PNA clamp tail is not clear. That is, it is not clear if the two are identical or if the PNA clamp tail is a narrower limitation. If the PNA clamp tail is different from the PNA molecule via a linker then it is not clear if the inclusion of the PNA clamp tail is meant to limit the claim or not.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi ('Recombinant PCR' In: PCR Protocols: A Guide to Methods and Applications. Edited by M. Innes *et al.* New York: Academic Press, 1990, p. 177-183) in view of Fakhfakh *et al.* (Journal of General Virology, 1996, 77:519-523).

Higuchi teaches methods in which two previously unrelated sequences can be joined (p. 178, and Fig. 3), for example, a promoter sequence can be joined to a gene. The method taught by Higuchi for the addition of a primer to a gene comprises a polymerase chain reaction amplification of a gene in the presence of a first DNA fragment (a promoter, F1), and a first primer which has a portion complementary to the gene and a portion complementary to the promoter (P3) (see figure 3). They further teach a step in which the resulting product would be amplified again using primers complementary to the ends of the molecule, called "outside primers) (P1, for example) (see Figure 1).

Higuchi does exemplify the use of this method wherein a promoter and a terminator sequence are added to one DNA molecule to produce a transcriptionally active DNA molecule.

At the time the invention was made, however, it was routine in the art to add both a terminator and a promoter to a DNA molecule in order to produce a transcriptionally active fragment for expression of the DNA of interest. For example, Fakhfakh *et al.* teach methods in which a both a terminator and a promoter are added to a gene in order to produce a transcriptionally active molecule (see for example, figure 1, and p. 520-521).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the method taught by Higuchi to add a promoter and a terminator onto a DNA fragment, as is exemplified by Fakhfakh *et al.* The ordinary practitioner would have been motivated to use the methods of Higuchi for such an addition because Higuchi specifically states that "For more complex DNA constructs, serial applications of this principle provide a convenient alternative to cycles of conventional fragment purification, ligation, cloning, and screening and growing clones (p. 180)."

5. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi in view of Fakhfakh *et al.* as applied to claim 1 above, and further in view of Crowley (US 5561053).

The teachings of Higuchi in view of Fakhfakh *et al.* are applied to claim 2 as discussed above. Higuchi *et al.* in view of Fakhfakh *et al.* do not teach the use of this method with the cytomegalovirus IE promoter.

However, the use of the cytomegalovirus IE promoter for the production of transcriptionally active fragments was routine in the art at the time the invention was made. For example, Crowley teaches that the human cytomegalovirus immediate early promoter has been identified as a eukaryotic promoter that is strong for high-level expression of a downstream DNA (Col. 2, lines 8-21).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the cytomegalovirus IE promoter when producing a transcriptionally active fragment since it was known to be a promoter that is strong for high-level expression of downstream sequences.

6. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi in view of Fakhfakh *et al.* as applied to claim 1 above, and further in view of Lin (US 5621080).

The teachings of Higuchi in view of Fakhfakh *et al.* are applied to claim 2 as discussed above. Higuchi *et al.* in view of Fakhfakh *et al.* do not teach the use with a therapeutic gene.

However, the expression of therapeutic genes using transcriptionally active DNA molecules was routine in the art at the time the invention was made. For example, Lin describes the production of erythropoietin from a transcriptionally active DNA (Example 7, Col. 23-25). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention

was made to have produced a transcriptionally active fragment containing a therapeutic gene using the methods taught by Higuchi in view of Fakhfahk *et al.* in order to have provided a fragment which can be used for the expression and recovery of a useful protein, such as is taught by Lin.

7. Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higuchi in view of Fakhfakh *et al.* as applied to claim 1 above, and further in view of Felgner *et al.* (US 6165720).

The teachings of Higuchi in view of Fakhfakh *et al.* are applied to claim 2 as discussed above. Higuchi *et al.* in view of Fakhfakh *et al.* do not teach the use of the cytomegalovirus IE promoter, the use of a therapeutic gene or addition of PNA clamp tails to the transcriptionally active molecules.

Felgner *et al.* teach PNA "clamps" which have two identical PNA sequences joined by a flexible hairpin linker (Col. 2, lines 31-34). They teach that the addition of a PNA clamp to a transcriptionally active DNA molecule improves the delivery and expression of DNA both in vitro and in vivo (Col. 6, lines 53-54). Felgner *et al.* exemplify this method in the creation of a transcriptionally active fragment which has the CMV IE promoter and a PNA clamp (Example 22, Col. 26). Further, Felgner *et al.* teach that plasmids may be designed to include a therapeutic gene and the PNA conjugation methods described may be used to increase transfection efficiency, nuclear localization and expression of a therapeutic gene for gene therapy applications (Col. 9, lines 61-64).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have constructed transcriptionally active fragments with the

cytomegalovirus IE promoter as taught by Felgner *et al.* because Felgner *et al.* teach that the cytomegalovirus IE promoter "is considered one of the strongest promoters active in a broad range of mammalian cells and tissues (Col. 26, line 66-Col. 27, line1). Further It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have created a construct comprising a therapeutic gene in order to have provided a method for producing the gene product, either in vitro or in vivo. Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have placed PNA clamps on the ends of the transcriptionally active DNA molecules since Felgner *et al.* teach the benefits of such inclusion, including "increased transfection efficiency, nuclear localization, transcription activation, endosomal lytic activity and immunostimulatory activity (Col. 6, lines 32-35)."

Allowable Subject Matter

8. Claims 7 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

January 4, 2001